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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,020	03/13/2001	Zurit Levine	2786-0168P	9282

2292 7590 04/14/2004

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EXAMINER	
HUFF, SHEELA JITENDRA	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,020	LEVINE ET AL.	
	Examiner	Art Unit	
	Sheela J Huff	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-2, 5-12, 13(in-part), 16 and 19-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-4, 13(in-part)-15, 17-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group XXXVI, claims 3,4 13(in-part)-15 and 17-18 in Paper No. 3/9/04 is acknowledged. The traversal is on the ground(s) that the Examiner has failed to establish that consideration of a reasonable number of sequences is an undue burden. This is not found persuasive. Applicant is directed to page 6-top of the restriction. Each sequence is distinct in sequence and searching every one of them would be an undue burden.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 101/112

Claims 3-4, 13(in-part)-15 and 17-18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The claims amino acid sequence and composition claims depending on the sequence are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. A protein could be used in conducting research to functionally characterize the protein. The need for such research clearly indicates that the protein and/or its function are not disclosed as to a currently available or substantial utility. A starting material that can be only be used to produce a final product does not have substantial asserted utility in those instances where the final

product is not supported by a substantial utility. In the case Seq ID NO. 72 and the amino acid encoded by SEQ ID No. 36 that may be produced as final products have identified substantial utilities. The research contemplated by applicants to characterize potential protein products, especially their biological activities, does not constitute a substantial utility. Identifying and studying the properties of a protein itself of the mechanisms in which the protein is involved does not define a "real world" context or use. Similarly, the other listed and asserted utilities in the instant specification are not substantial due the being generic in nature and applicable to a myriad of such compounds. Note, because the claimed invention is not supported by a substantial asserted utility for the reasons set forth above, credibility has not been asserted. Neither the specification as filed not any art of record discloses or suggests any property or activity for the amino acid sequence such that another non-asserted utlity would be well established for the compounds.

It is noted that applicants apparently have identified that the variant sequences may be a kinase, whereas others of the identified variants are not kinases (see Table starting at page 23). However, because no SEQ ID NO. have been inserted into the Table it is possible that that currently claimed sequence is not a kinase. Even if the currently claimed sequence is a kinase, this has been established by sequence analysis. Absent objective evidence, one skilled in the would have reasons to doubt that sequence similarly alone would reasonable support the assertion of biological activity. Furthermore, it is unclear whether the similar sequence identified in the prior art has actually been tested for the biological activity or whether this also is an asserted

biological activity because upon sequence similarity to yet a different sequence. Note that it would have been known in the art that sequence similarity does not reliably result in similar or identical biological activities. For example, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search

(p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2).

Furthermore, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Claims 3-4, 13(in-part)-15 and 17-18 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

Claims 3-4, 13(in-part)-15 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having 90% identity with Seq ID NO. 72 and the amino acid encoded by SEQ ID No. 36 or homologues thereof. While the amino acid sequence of SEQ ID NO:72 is adequately described in the specification as-filed, thereby providing an adequate basis for the polypeptide of SEQ ID NO:72; there is insufficient written description as to the identity of a polypeptide having at least 90% sequence identity to SEQ ID NO:72 that would still maintain the function of the polypeptide. Consequently, the specification does not provide an adequate written description of a polypeptide having at least 90% sequence identity to SEQ ID NO:72.

The specification as filed does not provide adequate written description support for a ~~antibody to~~ a polypeptide having at least 90% sequence identity to SEQ ID NO:72. Polypeptides having diverse functions are encompassed by the phrase 90% identity. Thus a broad genus having potentially highly diverse functions is encompassed by the phrase 90% sequence identity" and conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. For example, Skolnick et al. (Trends in Biotech., 18(1):34-39,

2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only SEQ ID No. 72 meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claims 13(in-part)-15 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in In Re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex Parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the breath of the claims,
5. the amount of direction or guidance present, and
6. the presence or absence of working examples.

The following is an analysis of these factors in relationship to this application.

Applicant discloses and claims a pharmaceutical composition comprising Seq ID NO. 72 and the amino acid encoded by SEQ ID No. 36 or homologues thereof the use of this composition to treat or cure any disease "which can be ameliorated or cured by raising the level" of the claimed amino acid. Applicant does specifically mention the treatment of cancer.

However, the state of the art does not recognize that the claimed sequences or even homologous sequences can readily be used in the treatment or cure of any disease or cancer. In fact, applicant states that the claimed sequences are derived from tumor-involved genes and that the sequences "may have the same physiological activity as the original tumor-involved peptide" or "may have an opposite physiological activity from the activity features by the original tumor-involved peptide" or "may have a completely different, unrelated activity to the activity of the original tumor-involved peptide" or "may be no activity at all" (page 12 bottom of specification). In fact, the state of the art and applicant are not sure what the peptides do.

Applicant's have not provided any guidance or working examples in the specification as to how the claimed sequences can treat or cure cancer or any and all diseases. There is no objective evidence to show that the claimed sequences have any effect. In fact, the specification is highly prophetic. Even if applicant did provide in vitro assays, the claims are directed to in vivo treatments and such treatments, in and of themselves, are unpredictable because pharmacokinetic factors such as the stability of the peptides in the body, half-life, absorption efficiency, binding affinity for target cells, biotransformation, and the rate of clearance from the body are important consideration for the efficacy of the claimed subject matter and yet have not been considered. In the absence of these considerations, there is no assurance (ie. it is unpredictable) that the active sequences would be available in effective doses at the target sites and for periods of time sufficient to effect the required cellular or biological responses.

Applicant basis the potential use of the claimed sequences on sequence homology and as discussed above in Bork this is not highly accurate. Even if the seqeunce could be definitely correlated to one disease, it is highly unbelievable that the seqeunce could be correlated to any and all disease and any and all types of cancer.

Applicant further claims that the disease can be "cured". This implies 100% prevention and applicant has not provided any objective evidence to show that sequences can abolish any acitivty or disease.

In view of the above, it is the Examiner's position that one skilled in the art could not make and/or use the invention without undue experimentation.

Claims 3-4, 13(in-part)-15 and 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 depends on a non-elected claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Tuesday 5:30am-11:30am and Fridays 6:00am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheela J. Huff

Sheela J Huff
Primary Examiner
Art Unit 1642

sjh